

# Myopathy with hypophosphatasia

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## Abstract

**Three children with hypophosphatasia also had muscle pains, stiffness, and symptoms of proximal lower limb muscle weakness that occurred early in the disorder and were the presenting features in two. A non-progressive myopathy may be an important sign of hypophosphatasia.**

The clinical features of hypophosphatasia, an inherited metabolic bone disorder, include defective bone mineralisation, skeletal abnormalities, premature cranial synostosis, and premature loss of deciduous teeth.<sup>1</sup> Plasma and tissue activities of the bone/liver/kidney alkaline phosphatase isozyme are low. Urinary excretion and plasma concentrations of phosphoethanolamine and inorganic pyrophosphate are high. Infantile, childhood, and adult forms have been described.<sup>1</sup>

We report three unrelated children with a childhood form of hypophosphatasia who also had proximal muscle weakness, a finding not previously recognised as a feature of this disorder.<sup>1</sup>

## Case reports

### CASE 1

This child was first seen at another hospital at the age of 2.5 years because of delayed motor activity milestones, difficulty in walking, and inability to climb stairs; he had mild proximal muscle weakness. Electromyographic examination suggested a muscle disorder and he was thought to have a congenital myopathy. A diagnosis of hypophosphatasia was subsequently made because of abnormal dentition, low serum alkaline phosphatase activity, and severe osteopenia on radiography. We saw him at the age of 5.5 years at which time the motor symptoms were unchanged. In addition, he also complained of pain and stiffness in the leg muscles, more pronounced in the mornings and during cold weather. On examination his height, weight, and head circumference were at the 10th, 5th, and 60th percentiles, respectively, as they had been on previous measurements. He had mild (grade 4/5) proximal muscle weakness, a waddling gait, and difficulty in getting off the floor and in climbing up stairs. The muscles were not tender. Deep tendon reflexes were normal. Serum creatine kinase activity was normal on several occasions. Electromyography showed minor abnormalities compatible with a myopathy. Motor and sensory nerve conduction studies were normal.

When last seen at the age of 9.5 years he still had difficulty in climbing stairs and mild proximal muscle weakness. Muscle pains were no longer severe.

### CASE 2

This boy was first seen at the age of 9.5 years because of severe pains in the muscles of his lower limbs. He had had difficulty in walking and climbing stairs since early childhood. On examination his head circumference, height, and weight were at the 75th percentile. He had mild (grade 4/5) proximal muscle weakness, and a waddling gait. He had difficulty in getting off the floor and in climbing up stairs. Deep tendon reflexes were normal. There was no muscle tenderness. Serum creatine kinase activity was normal on several occasions. He had the characteristic radiological and biochemical findings of hypophosphatasia. Electromyography at the ages of 9.5 and 12 years suggested a myopathy. Motor and sensory nerve conduction studies were normal. The muscle pains became less severe when he was about 13 years old, although mild proximal muscle weakness persisted. He was last seen at the age of 17. He no longer had pain, but continued to have difficulty in going up stairs.

### CASE 3

This boy was referred for neurological assessment at the age of 3 years because of an awkward gait and muscle pains. His limbs had been floppy when he was an infant. He started to walk when he was 13 months old. He subsequently had difficulty in arising from the floor, and climbing up stairs without support. He was not able to run. He had also been complaining of pain and stiffness in the muscles of his legs since he was 1 year old. The pain and stiffness were particularly severe after physical activity and in damp or cold weather. A diagnosis of hypophosphatasia had been made at the age of 1 year because of premature loss of deciduous teeth and the characteristic biochemical and radiological features. He had also developed craniostylosis for which craniectomies were performed. On examination his head circumference was at the 40th percentile, and his height and weight were around the 50th percentile. He had mild (grade 4/5) proximal weakness in the lower limbs. Coordination was normal. The muscles were not tender. The deep reflexes were present. He had a positive Gowers' sign and found it difficult to climb stairs without support. His gait was waddling. Serum creatine

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Biochemical findings in three children with hypophosphatasia at different ages (years)

	Serum alkaline phosphatase activity (U/l)	Serum calcium concentration (mmol/l)	Serum phosphate concentration (mmol/l)	Serum creatine kinase activity (U/l)	Urinary phosphoethanolamine concentration ( $\mu$ mol/mmol creatinine)
Control values	70–258 (1–10 years) 59–422 (10–16 years)	2.0–2.6	1.29–2.26	36–188	<10
Case No 1					
4.5	27	2.4	1.8	107	141
6.5	27	2.4	1.8	80	141
8.5	28	2.4	2.1	100	Not measured
Case No 2					
9	37	2.3	1.9	76	45
13	35	2.5	2.1	Not measured	Not measured
17	17	2.6	1.6	150	Not measured
Case No 3					
1	40	2.4	2.0	Not measured	150
3	57	2.6	1.8	200	Not measured

kinase activity on a random sample was 200 U/l (normal range 36–188). Permission to carry out electromyography and muscle biopsy was refused.

### Laboratory investigations

Biochemical findings are summarised in the table.

### MUSCLE BIOPSY SPECIMENS

Biopsy specimens of the left quadriceps muscle of case 1 taken at the age of 7.5 years, and the right gastrocnemius and left quadriceps muscles of case 2 taken at the ages of 10 and 14 years, respectively, were examined by light microscopy, histochemistry, and electron microscopy.

The average myofibre diameter was about 60% of normal in case 1 and about 85% of normal in case 2. Isolated small structurally abnormal myofibres were seen in the biopsy specimens from both children.

### Discussion

The radiological and biochemical findings in our patients were characteristic of hypophosphatasia. All three had symptoms secondary to proximal lower limb muscle weakness, muscle pains, and stiffness from the time they began to walk. These were the presenting symptoms in cases 1 and 2, and case 1 was initially diagnosed as having a congenital myopathy. Such a presentation has not been reported in hypophosphatasia. Although the possibility of a myopathy was not considered in case 3 when the diagnosis of hypophosphatasia was made at the age of 1 year, the history suggests that muscle impairment was a feature at that time.

The symptoms in our cases could not be explained by skeletal impairment. Their clinical features resemble those in osteomalacia myopathy.<sup>2–5</sup> Muscle weakness has also been described with phosphate deficiency.<sup>6</sup> The serum creatine kinase activity is generally normal in osteomalacia myopathy, as it was in two of our three cases. Two of 23 patients

reported by Dastur *et al* had mildly increased serum creatine kinase activity.<sup>3</sup> This was slightly raised on a single random sample in our third case, a finding of uncertain relevance. Only minor morphological abnormalities were found in the biopsy specimens of cases 1 and 2. The contrast between the apparently scanty pathological findings, and the more pronounced clinical symptoms in our cases with hypophosphatasia is also a feature of osteomalacia myopathy.<sup>5</sup> The cause of the myopathy in osteomalacia has not been identified.

We cannot provide a clear explanation for the myopathy in our cases of hypophosphatasia. The precise role of alkaline phosphatase in promoting normal bone formation is still controversial; in general terms, the enzyme hydrolyses monophosphate esters at the epiphyseal plate and in membranous bone. Inorganic phosphate is thereby made available for the formation of hydroxyapatite crystals.<sup>1</sup> Alkaline phosphatase activity has been shown in the walls of capillaries and in the muscular and intimal coats of large vessels, but not in skeletal muscle.<sup>7</sup> Serum calcium and phosphate concentrations were normal in our patients but it is possible that the intracellular concentration of phosphate was altered in muscles.

A non-progressive proximal myopathy with muscle pains and stiffness may be an important and early sign of hypophosphatasia, which with other osteomalacic syndromes, should be considered in children presenting with such a myopathy.

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